The Examiner has rejected claims 24-30 under 35 U.S.C. § 112, first paragraph, for nonenablement. The Examiner asserts that the specification has no working examples demonstrating enablement of the claimed invention. The Examiner asserts that the goal of peptide immunotherapy of T-cell-mediated autoimmunity is to reduce anergy in self reactive T cells. The Examiner cites Wraith et al. (*Cell* **59**: 247-255 (1989)) for the teaching that inhibition of the response restricted by one class II molecule may lead only to the escape to an autoimmune response to a separate epitope restricted by a different class II molecule. The Examiner also cites Tisch et al. (*Proc. Natl. Acad. Sci.* **91**:437-438 (1994)) for the teaching that treating an ongoing T-cell-mediated autoimmunity by administering an antigen peptide may have an immunizing effect and exacerbate the disease condition. The Examiner concludes that, in the absence of working examples of the efficacy of the peptides in treating already established multiple sclerosis patients, it would require undue experimentation to practice the claimed invention.

Applicants note that the presence of working examples demonstrating enablement is not a requirement for patentability. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include, but are not limited to:

1. the breadth of the claims,
2. the nature of the invention,
3. the state of the prior art,
4. the level of one of ordinary skill,
5. the level of predictability in the art,
6. the amount of direction provided by the inventor,

7. the existence of working examples, and
8. the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands,* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

It is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The Examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole. Id. at 737 & 740, 8 USPQ2d at 1404 & 1407.

The present specification contains precise instructions on how to construct the peptides to be used, how and to whom to administer these, and what effects are to be expected. This is sufficient for the skilled worker to reproduce the invention, and thus the invention is enabled. The fact that certain prior art documents contain statements that can be interpreted as casting *a priori* doubt on the success of comparable, but not identical, approaches does not detract from the production of enablement from the instructions provided.

The Examiner states that "in endogenous peptide therapy, the goal of peptide immunotherapy of T-cell-mediated autoimmunity is to induce anergy in self-reactive T cells." Although this may be the goal of some research groups, such as Wraith et al., who aim at peptides that block MHC, this is not the goal of the present invention. The hsp peptide therapy of the present invention aims to induce and strengthen regulatory T cells, which subsequently downregulate pathogenic autoreactive T cells in their environment. The inventors do not regard T cells specific for hsp peptides as pathogenic; instead, they have found that reactivity towards hsp is associated with disease remission, which is based on the

activation of T cells capable of responding to the shared epitope in self hsp60 (see e.g. p. 27, lines 29-34 of the specification). It may also be noted that the therapy of the present invention does not use "endogenous peptides", but, instead, microbial, i.e. exogenous peptide having a specified degree of homology with endogenous peptide. Thus, the potential pitfalls and side-effects of antigen peptides recognized by the self-reactive pathogenic T cells do not hold for the claimed invention on hsp-peptide therapy, or at least cannot be used as evidence of lack of enablement of the invention. The sentence from Wraith et al. quoted by the Examiner does not represent a finding by the authors, but only a theoretical possibility among "several potential difficulties" of "using MHC blocking peptides". Also, the citation of Tisch et al. (p. 437, column 3) merely relates to a possibility that may or may not be realistic and is not supported by experimental data.

In summary, even if doubt expressed in the prior art is allowed to be used as an argument for nonenablement, the doubts expressed by the prior art in this case are highly speculative and unsupported, and cannot reasonably be used to neutralize or invalidate the clear experimental indications contained in the specification that the invention does work (see, in particular, pages 18 and 19 of the specification). These indications have been supported by subsequent animal studies. As an example, the attached figure shows that a peptide covered by the invention (peptides 253-268) inhibits progression of atherosclerotic lesions in a mouse model. Recent articles from the research group of the inventors can be provided showing further evidence.

The Examiner also asserts that the recitation of "peptides comprising at least 5 amino acids which are identical with corresponding amino acids in the same relative position in a T cell epitope of said mammalian stress protein" has not been enabled. The Examiner asserts that this definition encompasses large numbers of peptides that have not been shown

to function according to the claims. The Examiner cites Karin et al. (*J. Exp. Med.* **180**: 2227-2237 (1994)) as teaching that substitution of phenylalanine for alanine at adjacent positions of a peptide produced induction or no induction of EAE in rats (an animal model of multiple sclerosis), respectively. The Examiner concludes that the effects of amino acid changes on peptide-MHC binding, T cell proliferation, and *in vivo* effects of these peptides are unpredictable, and that it would require undue experimentation to practice the claimed invention on the basis of the current recitation.

Applicants note that the limitation to "peptides comprising at least 5 amino acids which are identical with corresponding amino acids in the same relative position in a T cell epitope of said mammalian stress protein" in claim 24 of the application is followed by a limitation to "said epitope and said part containing at least 4 consecutive amino acids which are identical with the corresponding mammalian stress protein amino acids". Substitutions of the type described by the Examiner in the Office Action do not enter into this selection process. When determining whether, as stated in claim 24, the particular part of a microbial protein and its mammalian homologue are sufficiently homologous, the at least 5 amino acids within this part and the at least 4 consecutive amino acids should be identical, not just similar. Only after the homology has been established, and the part of the microbial protein has been subsequently identified, one or more amino acids may be exchanged with similar amino acids. Even then, the particular part should still comprise a T cell epitope corresponding to a T cell epitope of the mammalian homologue. It is believed not to be an undue burden for the skilled worker to test whether the finally selected peptide induces T-cell reactivity.

The Examiner asserts that the substitution of a single peptide can produce unforeseeable effects, but Applicants have provided guidance in this regard in both the claims and the specification. The specification clearly indicates, at page 8, lines 16-32, what is to be

understood by the use of the term "similar". In addition, Applicants note that individual peptides are well characterized in the art with respect to properties such as size, charge, and hydrophilicity, and that the relationship of these properties to protein structure is well known. Claim 29 also refers to properties of individual peptides, limiting replacement to peptides with size, charge and polarity similar to the peptide being replaced. The Examiner's cited replacement of alanine with phenylalanine involves two species that may have some charge and nomenclatural similarities, but the two species differ widely in size and polarity, as well as side chain orientation. Substitution of phenylalanine for alanine would not be expected to produce a new species with similar properties, is not taught by the specification, and is not within the scope of claim 29.

For these reasons, claims 24-30 are believed to be enabled and in condition for allowance. Reconsideration of the rejections and allowance of the claims are requested.

Respectfully Submitted,

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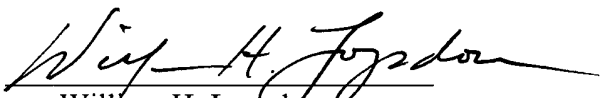
By 

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